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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,838	11/29/2001	Hans Hofland	P 23,643-A USA	6395

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,838	HOFLAND ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,11,14,15,18-23 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,11,14,15,18-23 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

2. The after-final amendment filed 8/18/06 was entered. Claims 1, 7, 11, 14-15, 18-32 are presently pending.

3. The following action will address Applicant's arguments set forth in the Pre-Appeal Brief Request for Review filed 10/16/06.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

5. In the Pre-Appeal Brief Request for Review filed 10-16-06 Applicants stated that pending claims 24-27 were erroneously were not identified. Contrary to Applicant's assertion's, although claims 24-27 were not indicated as rejected on the PTO-326, claims 24-27 were rejected in the Final Office Action under 35 USC 112, 1st paragraph.

Response to Amendment

Claim Rejections - 35 USC § 112

6. The rejection of claims 1, 7, 11, 14-15, and 18-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (New matter), is withdrawn.

Claim Rejections - 35 USC § 102

7. Claims 18-23, and 30 remain rejected under 35 U.S.C. 102(e) as being anticipated by Monahan et al., or unpatentable over Monahan et al. for the reasons of record set forth in the Final Office Action mailed 3-09-05.

Applicant's arguments filed 8-18-06 have been fully considered, but they are not persuasive. Applicants traversed this rejection on the grounds that "[a]pplicant's colloid clearly distinguishes structurally from that disclosed in the prior art in that it does not require the presence of an additional layer of anionic lipids or anionic polymers around the DNA-containing complex the colloid of the prior art does. Inasmuch as the traversal argument is contingent upon the amendment of the August 2006 reply, the examiner's maintenance of the rejection is in clear error." Contrary to Applicant's assertions, as stated in the prior Office Action, absent evidence to the contrary, since claim 18 is drawn to "a stable colloid," regardless of its method of preparation, if the prior art compound reads on a process which involves the production of a "stable colloid," the claim is unpatentable even though the prior art product was made by a different process. See MPEP § 2113 [R-1], Product-by-Process Claims: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

Monahan et al. anticipates the instantly claimed invention, since they disclose a process for the formation of a stable colloid, wherein said process comprises that the addition of citraconic anhydride to the cationic polymer poly-L-lysine, and the formation of citraconylpoly-L-lysine, and the addition of this compound to a complex of DNA and poly-L-lysine, wherein the overall zeta potential of the formed particles of this reaction is negative (see col. 25, lines 27-65). Additionally, Monahan et al. teach the use of NHS ester to react with cationic polymers to form anionic polymers. Additionally, it is clear that the invention of Monahan et al. is specifically designed for modifying DNA-polymer complexes to comprise a negative zeta potential for the express purpose of delivering nucleic acid in cells (see abstract).

Claim Rejections - 35 USC § 103

8. Claims 1, 7, 11, 14-15, 18-23, and 28-32 remain rejected and claims 24-27 are rejected under 35 USC § 103(a) as being unpatentable over Semple (US Patent No. 6,287,591 B1) taken with Trubetskoy (US 2003/0026841 A1) and Monahan et al. (6,379,966), for the reasons of record set forth in the Final Office Action mailed 3-09-2005, and those reasons set forth below.

Applicant's arguments filed 8-18-06 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the examiner has not established a *prima facie* case of obviousness, since the examiner has not shown that one skilled in the art would have had a reasonable expectation of success that the invention as claimed would work for its intended purpose. Moreover, Applicants argue that they have provided evidence as to why there should not be such an

expectancy by pointing out that Trubetskoy et al. states that the addition of anionic compounds to a complex containing DNA and cationic lipids or cationic polymers could lead to destabilization of the complex. The evidence that Applicants are relying upon is found in Trubetskoy et al. (US 2003/0026841), paragraph [0043], this passage of Trubetskoy et al. is duplicated below:

> **[0043]** We have demonstrated that similar layering of polyelectrolytes can be achieved on the surface of DNA/polycation particles (V S Trubetskoy, A Loomis, J E Hagstrom, V G Budker, J A Wolff. Nucleic Acids Res. 27:3090-3095, 1999). The principal DNA-polyeation (DNA/pC) complex used in this study was DNA/PLL (1:3 charge ratio) formed in low salt 25 mM HEPES buffer and recharged with increasing amounts of various polyanions. The DNA particles were characterized after addition of a third polyion component to a DNA/polycation complex using a new DNA condensation assay (V S Trubetskoy, P M Slattum, J E Hagstrom, J A Wolff, V G Budker. Anal. Biochem. 267:309-313, 1999) and static light scattering. It has been found that certain polyanions such as poly(methacrylic acid) and poly(aspartic acid) decondensed DNA in DNA/PLL complexes. Surprisingly, polyanions of lower charge density such as succinylated PLL and poly(glutamic acid), even when added in 20-fold charge excess to condensing polycation (PLL) did not decondense DNA in DNA/PLL (1:3) complexes. Further studies have found that displacement effects are salt-dependent. In addition, poly-L-glutamic acid but not the relatively weaker polyanion succinylated poly-L-lysine (SPLL) displaces DNA at higher sodium chloride concentrations. Measurement of ζ-potential of DNA/PLL particles during titration with SPLL revealed the change of particle surface charge at approximately the charge equivalency point. Thus, it can be concluded that addition of low charge density polyanion to the cationic DNA/PLL particles results in particle surface charge reversal while maintaining condensed DNA core intact. Finally, DNA/polycation complexes can be both recharged and crosslinked or caged U.S. 08/778,657, U.S. Ser. No. 09/000,692, U.S. Ser. No. 97/24089, U.S. Ser. No. 09/070299, and U.S. Ser. No. 09/464,871.

Contrary to Applicants assertions, although the above passage does state that compounds such as poly(methyacrylic acid) and poly(aspartic acid) were found to decondense DNA in DNA/PLL complexes, the passage further clearly states that compounds of lower charge density such as succinylated PLL and poly(glutamic acid),

even when added in 20-fold charge excess to condensing polycation (PLL) did not decondense DNA in DNA/PLL (1:3) complexes. The ordinary skilled artisan would have merely elected to use compounds of lower charge density particularly succinylated PLL or poly(glutamic acid) to modify a DNA/cationic lipid complex, and would therefore have avoided the problems previously found to be associated with using poly(methyacrylic acid) or poly(aspartic acid). Therefore contrary to Applicant's assertions, there is a reasonable expectation of success that the ordinary skilled artisan, following the combined teachings of Semple et al., Trubetskoy et al. and Monahan et al. would have produced the stable colloids according to the present invention.

Moreover, contrary to Applicant's assertions, one of ordinary skill n the art would have been motivated to modify the DNA-lipid compounds of Semple et al. with a compound that would reduce, remove or reverse the positive charges on the surface of the disclosed DNA-lipid compounds since Semple et al. (see col. 9) teach the following (as set forth in the Office Action mailed 9/09/04, see page 8):

> The methods and composition of the invention make use of certain lipids which can be present in both a charged and an uncharged form. For example, amino lipids which are charged at a pH below the pK_a of the amino group and substantially neutral at a pH above the pk_a can be used in a two-step process. First, lipid vesicles can be formed at the lower pH with (cationic) amino lipids and other vesicle components in the presence of nucleic acids. In this manner the vesicles will encapsulate and entrap the nucleic acids. Second, the surface charge of the newly formed vesicles can be neutralized by increasing the pH of the medium to a level above the pK_a of the amino lipids present, i.e., to physiological pH or higher. Particularly advantageous aspects of this process include both the facile removal of any surface adsorbed nucleic acid and a resultant nucleic acid delivery vehicle which has a neutral surface. Liposomes or lipid particles having a neutral surface are expected to avoid rapid clearance from circulation and to avoid certain toxicities which are associated with cationic liposome preparations.

The teachings of Semple et al. clearly suggests modifying the surface of DNA/cationic lipid particles containing formulation, the particles would resist degradation from *in vivo* circulation and not produce certain toxicities, which are associated with cationic liposome preparations. Along this same rationale, Trubetskoy et al. (see page 5, paragraph 52) Monahan et al. (col. 23) provide motivation for a recharging process as applied to reducing the cationic charge on liposomal vessels, to thereby enhance the efficiency of gene transfer *in vivo*. Moreover, the very reagents that Applicants use for "recharging" the cationic charge on the recited cationic lipids or polymers present in said complex are disclosed in Monahan et al. (CCA and NHS ester), for use in the same purpose, namely for the treatment of cationic polymers to confer a negative charge in the design of a stable DNA-lipid complex for delivery into a cell. Furthermore, Trubetskoy et al. teaches that an addition of polyanionic molecules to a lipid/DNA complex would enhance the transfer activity of a DNA/cationic lipid complex.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 11 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 14-15, 21-23, 25-27, 30 and 32, recites the phrase "said complex," however the term "said complex" is vague and indefinite since it is unclear which

complex applicants are referring to since claim 1 line 2 recites "a complex", and line 5 recites "a complex." Additionally, claims 11, 21, and 25, further recites "wherein said complex further comprises a targeting ligand covalently attached to a cationic lipid or polymer." The metes and bounds of this phrase are vague and indefinite since it is unclear if the targeting ligand is covalently attached to an additional cationic lipid or polymer or to the cationic lipid or polymer in the complex of the precursor colloid recited in claim 1.

Claim Objections

11. Claim 1 is objected to because of the following informalities: Claim 1 recites the limitation "N-hydroxysuccimide acetate," this term is improperly spelled, the correct spelling should be "N-hydroxysuccinimide acetate." (see for example original claim 8). Appropriate correction is required.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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JLE